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Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes

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Abstract

BACKGROUND—The comparative effectiveness of glucose-lowering medications for use with metformin to maintain target glycated hemoglobin levels in persons with type 2 diabetes is uncertain.

METHODS—In this trial involving participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%, we compared the effectiveness of four commonly used glucose-lowering medications. We randomly assigned participants to receive insulin glargine U-100 (hereafter, glargine), the sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or sitagliptin, a dipeptidyl peptidase 4 inhibitor. The primary metabolic outcome was a glycated hemoglobin level, measured quarterly, of 7.0% or higher that was subsequently confirmed, and the secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5%.

RESULTS—A total of 5047 participants (19.8% Black and 18.6% Hispanic or Latinx) who had received metformin for type 2 diabetes were followed for a mean of 5.0 years. The cumulative incidence of a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome) differed significantly among the four groups ($P<0.001$ for a global test of differences across groups); the rates with glargine (26.5 per 100 participant-years) and liraglutide (26.1) were similar and lower than those with glimepiride (30.4) and sitagliptin (38.1). The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. There were no material differences with respect to the primary outcome across prespecified subgroups defined according to sex, age, or race or ethnic group; however, among participants with higher baseline glycated hemoglobin levels there appeared to be an even greater benefit with glargine, liraglutide, and glimepiride than with sitagliptin. Severe hypoglycemia was rare but significantly more frequent with glimepiride (in 2.2% of the participants) than with glargine (1.3%), liraglutide (1.0%), or sitagliptin (0.7%). Participants who received liraglutide reported more frequent gastrointestinal side effects and lost more weight than those in the other treatment groups.

CONCLUSIONS—All four medications, when added to metformin, decreased glycated hemoglobin levels. However, glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target glycated hemoglobin levels. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; GRADE ClinicalTrials.gov number, NCT01794143.)

Type 2 diabetes affects more than 30 million adults in the United States and more than 500 million worldwide, with an annual incidence in the United States of approximately 1.5 million cases.[1,2] Its major human and economic costs are caused primarily by the development of diabetes-specific complications, including retinopathy, nephropathy, and neuropathy, and a risk of cardiovascular disease that is two to five times as high as that among persons without diabetes.[3] The long-term diabetes-specific complications have been ameliorated by interventions that decrease chronic glycemia, as measured by glycated hemoglobin levels.[4,5] A target glycated hemoglobin level of less than 7.0% (<53.0 mmol per mole) has been established by consensus for most persons with type 2 diabetes, with the goal of decreasing morbidity.[6]

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Virtually all recommendations for the management of glycemia in persons with type 2 diabetes have included metformin as the first medication to be used, with a second medication added when needed to achieve or maintain a glycated hemoglobin level of less than 7.0%.[7,8] Unfortunately, there are few long-term comparator studies to guide the choice of a second glucose-lowering medication. The purpose of the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study was to examine the relative effectiveness of agents from four of the most commonly used classes of glucose-lowering medications, when added to metformin, in achieving and maintaining target glycated hemoglobin levels in persons with recent-onset type 2 diabetes.[9] Here, we report the major glycemic outcomes of this trial. In our accompanying article in this issue of the *Journal*, we report the effects of the randomly assigned interventions on prespecified secondary outcomes (microvascular complications and cardiovascular events and their risk factors).[10]

METHODS

TRIAL DESIGN AND OVERSIGHT

This multicenter, parallel-group, comparative-effectiveness clinical trial was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health and designed by a subgroup of the investigators with NIDDK participation.[9] Randomization was conducted with the use of a centralized Web-based system and stratified according to trial site. The participants and clinic staff were aware of the treatment assignments; however, the investigators at the laboratories and reading centers and the members of the adjudication committee were unaware of the treatment assignments and the identity of each participant.

All the data were collected and analyzed by the trial research group. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the Supplementary Appendix with the full text of this article at NEJM.org. The authors wrote the manuscript and made the decision to submit it for publication. No confidentiality restrictions were imposed by the sponsors.

The manufacturers contributed the trial medications under clinical-trial agreements with the NIDDK but had no role in the design, conduct, or analysis of the trial. An independent data and safety monitoring board appointed by the NIDDK oversaw the conduct of the trial. All participating centers obtained approval from local institutional review boards.

PARTICIPANTS

Participants with type 2 diabetes were recruited at 36 clinical centers (Section S1 in the Supplementary Appendix) with the goal of composing a cohort that was broadly representative of the population with type 2 diabetes in the United States according to race and ethnic group. Eligible participants had type 2 diabetes that had been diagnosed at or after the age of 30 years, with the exception of American Indians or Alaska Natives, in whom the age at diagnosis was at least 20 years.[9] At initial screening, the known duration of diabetes was less than 10 years, and the participants had received at least 500 mg of

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metformin per day without the use of other glucose-lowering medications for the previous 6 months and were willing to use injection therapy. During a run-in period of 6 to 14 weeks before randomization, the metformin dose was increased to at least 1000 mg per day, with a target maximal dose (one that could be taken without unacceptable side effects) of 2000 mg per day. Eligible participants had a glycated hemoglobin level of 6.8 to 8.5% (50.8 to 69.4 mmol per mole) at the end of the run-in period.

TREATMENTS

The four medications selected for the current trial had to be approved by the Food and Drug Administration (FDA) and had to be in common use in combination with metformin at the time of the trial launch in 2013. Immediate-release or extended-release formulations of metformin (Bristol Myers Squibb) were supplied to all the participants. The randomly assigned treatment doses were adjusted on the basis of their labeling.

The treatments included the following: insulin glargine U-100 (hereafter, glargine) (Sanofi), administered daily at an initial dose of up to 20 U and adjusted according to glucose levels monitored by the participant and to avoid hypoglycemia; the sulfonylurea glimepiride (Sanofi), increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels monitored by the participant and to avoid hypoglycemia; the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (Novo Nordisk) initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects; and the dipeptidyl peptidase 4 inhibitor sitagliptin (Merck) at a dose of 100 mg, with the dose adjusted according to kidney function.

The assigned treatment was continued until the participant had a confirmed glycated hemoglobin level greater than 7.5% (>58.5 mmol per mole) (the secondary metabolic outcome) (Fig. S1 in the Supplementary Appendix). At that time, glargine was added to the three assigned noninsulin treatments. In participants assigned to receive glargine who had a secondary outcome event and those in the other three treatment groups who had a tertiary outcome event, described below, treatment was intensified by adding prandial rapid-acting insulin aspart to the glargine regimen, and the randomly assigned medications, with the exception of glargine, were discontinued.

Thiazolidinediones were not included in the trial because of safety concerns present at the time of trial planning; these concerns included bone loss, fluid retention, and a risk of bladder cancer with pioglitazone.[11] Sodium–glucose cotransporter 2 (SGLT2) inhibitors were not included because they had not been approved by the FDA in the United States during the planning and launch of this trial, and there was no clinical experience with them.

During the trial, consensus recommendations on the preferential use of GLP-1 receptor agonists and SGLT2 inhibitors in persons with prevalent cardiovascular disease or kidney disease were issued by the American Diabetes Association and the European Association for the Study of Diabetes.[12,13] These recommendations were communicated to participants with cardiovascular disease or kidney disease and to their health care providers. Any glucose-lowering medications other than those included as part of the trial were prescribed by the participants' own health care providers.

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OUTCOMES AND ASSESSMENTS

The participants were evaluated quarterly. The primary outcome was primary metabolic failure of the randomly assigned treatment, defined as confirmation (usually at the next quarterly visit) of a glycated hemoglobin level of 7.0% or higher.[9] A participant could first have a primary-outcome event at 6 months, with confirmation at 9 months, unless the glycated hemoglobin level was greater than 9.0% (>74.9 mmol per mole), in which case the outcome event could occur at 3 months with confirmation at 3 to 6 weeks thereafter. The secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5% after the primary outcome. The protocol stipulated initiation of glargine in the three noninsulin treatment groups and intensification of insulin therapy in the original glargine treatment group after a secondary-outcome event.[9] The tertiary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5% after the secondary outcome, regardless of whether glargine was initiated in the three noninsulin treatment groups and insulin therapy was intensified in the original glargine treatment group. All laboratory measurements were performed in the GRADE Central Biochemical Laboratory (Section S3).

In the comparisons of the four treatments, other important trial outcomes included the following: serious adverse events; targeted adverse events (severe hypoglycemia warranting treatment, as well as pancreatitis and pancreatic and other cancers, with the exception of nonmelanoma skin cancer) adjudicated by committee[9]; and effects on microvascular complications and cardiovascular disease and risk factors for these conditions.

STATISTICAL ANALYSIS

The analyses were conducted in accordance with the intention-to-treat principle. We estimated that a sample of 5000 participants, with an assumed hazard rate of 0.0875 per year for the primary outcome, would provide the trial with 90% power, corrected for six pairwise tests at the 0.05 level, to detect a 25% reduction in the risk of treatment failure among the groups. Kaplan–Meier plots were used to capture the cumulative incidence of outcomes according to the time from randomization to the visit at which an event was first reported and subsequently confirmed. We used a Cox proportional-hazards model to assess differences among the treatment groups, and the results are described with hazard ratios and robust confidence limits.[14] Differences in the outcomes were also reported as the restricted mean survival time,[15] or time to event, over 4 years of follow-up (when 85.8% of the trial cohort was followed). Additional analyses compared each treatment group with the other three combined with the use of hazard ratios and confidence intervals.[16]

For the primary outcome, a global log-rank test was used to test for any differences among the four groups, and additional tests were used to assess pairwise differences between groups. The closed-testing procedure provided protected P values for the six pairwise comparisons[17] and for the comparison of each treatment group with the other three combined.[16] The results of all other analyses were expressed as hazard ratios, estimates of effects (risk reductions), or mean values, all with accompanying 95% confidence intervals, or as simple percentages. The widths of the confidence intervals have not been adjusted for multiple testing, and any inferences drawn may not be reproducible; therefore, P values are not reported.

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Prespecified subgroup analyses included baseline factors as categories (age <45, 45 to 59, and ≥60 years; sex; and race or ethnic group) or strata in thirds (body-mass index [BMI; the weight in kilograms divided by the square of the height in meters], duration of diabetes, and glycated hemoglobin levels). Sensitivity analyses were conducted to assess the effect of coronavirus disease 2019 (Covid-19) and adherence to trial medications ("per-protocol analysis"). Details are provided in Figures S2 and S3.

RESULTS

BASELINE CHARACTERISTICS OF THE PARTICIPANTS

The first participant underwent randomization in July 2013, and the last participant underwent randomization in August 2017 (Fig. S4). The baseline characteristics of the 5047 participants, which were reported previously[18] and are shown in Table S1, included a mean (±SD) age of 57.2±10.0 years. A total of 63.6% were men, which reflected the inclusion of 10 Veterans Affairs medical centers as trial sites, and 41.5% of the participants were at least 60 years of age. A total of 65.7% of the participants identified as White, 19.8% as Black, and 3.6% as Asian. Ethnic group was also reported by the participants: 18.6% identified as Hispanic or Latinx, 2.7% as American Indian or Alaska Native, and 0.6% as Native Hawaiian or Pacific Islander.

The mean duration of diabetes as reported by the participants was 4.2±2.7 years. The daily metformin dose was 1576±525 mg at initial screening and 1944±205 mg at randomization, and 92.3% of the participants received 2000 mg per day. The mean BMI was 34.3±6.8, and the mean glycated hemoglobin level was 7.5±0.5% (58.3±5.3 mmol per mole). There were no substantial differences in any baseline demographic characteristic or findings on physical examinations or laboratory measurements among the four treatment groups. The baseline characteristics of the recruited cohort resembled those in the U.S. population who had type 2 diabetes that was being treated with metformin, who were of a similar age, and who had a similar duration of diabetes and a similar glycated hemoglobin range (Table S2).

PARTICIPANT RETENTION AND ADHERENCE TO TRIAL VISITS AND ASSIGNED MEDICATION

At the end of the trial in April 2021, the mean duration of follow-up was 5.0 years (range, 0 to 7.6), and 85.8% of the participants had been followed for at least 4 years. Retention and adherence were high; 94% of the participants completed a final visit, and they adhered to a mean of 92% of their expected trial visits (Table 1). A total of 27 of 5047 participants (0.5%) were lost to follow-up, and 153 died during the trial. During the Covid-19 pandemic, which overlapped with the trial closeout period, many visits were conducted by telephone and data on the glycated hemoglobin level were collected with the use of a validated mail-in kit.[19] As a result, 89% of all expected visits were completed during the final year of the trial (May 1, 2020, through April 30, 2021).

No differences were observed across the four treatment groups with respect to the retention of participants or adherence to trial visits (Table 1). Slight differences were observed with respect to metformin use, with 8% of the participants overall discontinuing

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metformin during study follow-up. There were differences in adherence to randomly assigned medications, with a higher frequency of discontinuation in the glimepiride and liraglutide groups (23% of the participants in each group) than in the sitagliptin (19%) and glargine (14%) groups. In the liraglutide and sitagliptin groups, most participants received the maximum doses of their assigned treatment; the mean daily maximum doses in the glimepiride and glargine groups were 5.4 mg and 51.4 U, respectively (Table 1 and Table S3). The percentage of participants who received nontrial glucose-lowering medications was highest in the glimepiride group (17%) and the sitagliptin group (15%), with less use of nontrial glucose-lowering medications in the liraglutide (11%) and glargine (14%) groups (Table S4).

EFFICACY

Table 2 shows the numbers of participants in each treatment group with a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome), a glycated hemoglobin level greater than 7.5% (the secondary metabolic outcome), and the corresponding rates, as well as the pairwise hazard ratios among the treatment groups, hazard ratios for each treatment as compared with the other treatments combined, and the restricted mean survival time (time to event). Details regarding the tertiary-outcome results are provided in Table S5.

Over the mean 5-year follow-up, 71% of the cohort had a primary metabolic outcome event, with the highest frequency in the sitagliptin group (77%), intermediate frequency in the glimepiride group (72%), and the lowest frequency in the liraglutide (68%) and glargine (67%) groups (Table 2). The between-group differences in the Kaplan–Meier estimates of the cumulative incidence of a primary-outcome event were significant ($P<0.001$ by the log-rank test) (Fig. 1A). During the first year of the trial, 55% of the participants in the sitagliptin group had a primary metabolic outcome event, as compared with fewer than 40% in the other groups. The differences in cumulative incidences over the first 4 years of the trial translated into 697 mean days to a primary metabolic outcome event in the sitagliptin group and 809, 861, and 882 days in the glimepiride, glargine, and liraglutide groups, respectively.

The six pairwise comparisons among the groups (Table 2) showed that the risk of a primary-outcome event was significantly lower with glargine than with sitagliptin (hazard ratio, 0.71, or a 29% risk reduction) and than with glimepiride (0.89, or an 11% risk reduction), with P values of less than or equal to 0.001 and 0.02, respectively, protected with the use of a closed testing procedure. The difference between the glargine and liraglutide groups was not significant. The risk of a primary-outcome event was 41% higher in the sitagliptin group than in the glargine group (hazard ratio in the sitagliptin group as compared with the glargine group, 1.41, which was obtained by inverting the hazard ratio in the glargine group as compared with the sitagliptin group [0.71]), 45% higher than in the liraglutide group, and 26% higher than in the glimepiride group ($P\leq0.001$ for all comparisons) (Table 2). The glimepiride group had a significantly lower risk of a primary-outcome event than the sitagliptin group and a higher risk than the glargine and liraglutide groups.

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The rates of secondary-outcome events (Table 2) and tertiary-outcome events followed a pattern that was similar to that for the primary outcome, with lower rates in the glargine and liraglutide groups, an intermediate rate in the glimepiride group, and the highest rate in the sitagliptin group. The Kaplan–Meier analyses of the cumulative incidences of the secondary-outcome events (Fig. 1B) and tertiary-outcome events (Fig. 1C) also resembled those of the primary-outcome events. A secondary-outcome event occurred in 55% of the participants in the sitagliptin group over a mean follow-up of 5 years, followed by glimepiride (in 50%), liraglutide (in 46%), and glargine (in 39%). The percentage of participants with a tertiary-outcome event increased slowly after the first year, reaching 27% at 4 years (Fig. 1C), with small differences among the groups and with the highest risk of a tertiary-outcome event in the glimepiride and sitagliptin groups and slightly lower risks in the glargine and liraglutide groups.

The mean glycated hemoglobin levels reached a nadir at 6 months in the glargine group and at 3 months in the other groups, with subsequent increases thereafter (Fig. 1D). At year 4, the absolute differences were small (Fig. S5), with mean glycated hemoglobin levels of 7.1% in the glargine and liraglutide groups as compared with 7.2% in the sitagliptin group and 7.3% in the glimepiride group.

SUBGROUP ANALYES

Prespecified subgroup analyses were performed to identify potential heterogeneity of the effects of the interventions. Table S6 describes the incidences of the primary and secondary metabolic outcome events in the treatment groups within subgroups. The risk of a primary-outcome event appeared to differ (increase) among the groups according to the increasing strata of baseline glycated hemoglobin level (Fig. 2). Even among participants in the lowest third of baseline glycated hemoglobin levels (6.8 to 7.2% [50.8 to 55.2 mmol per mole]), a glycated hemoglobin level of less than 7.0% was not achieved or maintained in approximately 60%.

The hazard ratio in the glargine group as compared with the sitagliptin group differed among the strata of glycated hemoglobin levels. The risk reductions with glargine increased among participants from the lower to highest strata of baseline glycated hemoglobin levels, from 17% (95% confidence interval [CI], 3 to 29) to 32% (95% CI, 19 to 42) to 46% (95% CI, 36 to 55). In participants with higher baseline glycated hemoglobin levels, sitagliptin was progressively less effective than the other three medications in maintaining or achieving a glycated hemoglobin level of less than 7.0%. In each glycated hemoglobin stratum, the risk of treatment failure with sitagliptin increased at a rate that was faster than that in the other groups as the glycated hemoglobin level increased. There was no suggestion of heterogeneity among the subgroups with respect to the secondary outcome.

SENSITIVITY ANALYSES

Results based on trial data from before the Covid-19 pandemic period (i.e., before March 15, 2020) showed that Covid-19 had no effect on the trial results as compared with the entire trial period. The results of per-protocol analyses, excluding data collected after the first instance of discontinuation of a trial medication (except for discontinuation in accordance

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with the protocol after a tertiary-outcome event) or initiation of a nontrial glucose-lowering medication, were similar to those in the intention-to-treat analyses with respect to the primary and secondary metabolic outcomes.

SERIOUS AND TARGETED ADVERSE EVENTS AND EFFECTS ON WEIGHT

Data on serious adverse events and prespecified targeted adverse events are provided in Figure 3. The glimepiride and glargine groups had a significantly higher overall incidence of any adverse event (serious adverse events and prespecified adverse events) (in 38% and 37% of the participants, respectively) than the liraglutide group (in 34%) (uncorrected P = 0.001 and P = 0.02, respectively). Severe hypoglycemia was generally uncommon, but it affected more participants assigned to glimepiride (2.2%) than to sitagliptin (0.7%) (P ≤ 0.001), liraglutide (1.0%) (P ≤ 0.001), or glargine (1.3%) (P = 0.02). There were no substantial differences among the treatment groups with respect to other targeted outcomes, including pancreatitis and pancreatic cancer (data not shown). Gastrointestinal symptoms were considerably more common with liraglutide than with the other three treatments. Over 4 years, the mean loss of weight was substantially higher in the liraglutide and sitagliptin groups (3.5 and 2.0 kg, respectively) than in the glargine and glimepiride groups (0.61 and 0.73 kg, respectively).

DISCUSSION

The overall results of the current trial highlight the difficulty in achieving and maintaining recommended glycated hemoglobin levels in participants with type 2 diabetes. In this diverse trial cohort, which included participants who were representative of those in the U.S. population who had metformin-treated type 2 diabetes of brief duration, the mean baseline glycated hemoglobin level was 7.5% (range, 6.8 to 8.5). During the mean 5-year follow-up, the target glycated hemoglobin level of less than 7.0% was not reached or maintained in 71% of the participants who received approximately 2000 mg of metformin per day plus one of four commonly used glucose-lowering medications. Even among participants with an initial glycated hemoglobin level of 6.8 to 7.2%, a glycated hemoglobin level of less than 7.0% was not maintained in approximately 60% of the participants over the 5-year follow-up. Although a glycated hemoglobin level of less than 7.0% was not achieved and maintained in most participants, the mean glycated hemoglobin levels did decrease in all the treatment groups over the course of the trial, and at the end of the trial these levels were approximately 0.3 percentage points lower than baseline levels.

The comparison of the trial medications revealed differences in efficacy and adverse effects. All four medications had an acceptable safety profile, as expected with FDA-approved medications. However, glargine and liraglutide were more effective at maintaining glycated hemoglobin levels in the target range over time. This translated into a glycated hemoglobin level of less than 7.0% for approximately a half year longer with glargine and liraglutide than with sitagliptin, which was the least effective treatment in maintaining target glycated hemoglobin levels. Glargine was most effective in maintaining the glycated hemoglobin level at 7.5% or lower, with only 39% of the participants having a glycated hemoglobin level greater than 7.5% (a secondary metabolic outcome event).

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The diverse trial cohort lent itself to comparisons among subgroups, including across race and ethnic groups for which there are disparities in diabetes care and outcomes.[20,21] All the participants had similar access to care and to medications for diabetes, which were provided at no cost to the participants, with no major differences in response to the treatments across any of the demographic subgroups with respect to the primary outcome. The only notable difference in the primary metabolic outcome according to baseline factors was observed in the analysis of three strata of glycated hemoglobin levels; participants with higher baseline glycated hemoglobin levels at baseline had progressively worse metabolic outcomes with sitagliptin than with the other treatments.

There were notable differences in other effects of the four medications. Although the overall incidence of severe hypoglycemia was low, glimepiride was associated with the highest incidence, followed by glargine. Participants who received liraglutide and sitagliptin had a mean weight loss of 3.5 kg and 2.0 kg, respectively, at 4 years, whereas the insulin and glimepiride groups had relatively stable weight. As expected,[22] participants in the liraglutide group reported the highest frequency of gastrointestinal side effects.

The strengths of the current trial include its design as a comparative-effectiveness trial that used approved medications according to labeling, as well as its large size, diverse population, and long duration. The only other comparative-effectiveness trial of similar scale involving participants with type 2 diabetes was ADOPT (A Diabetes Outcome Progression Trial),[23] which compared three monotherapies in participants with recent-onset type 2 diabetes. In clinical practice, metabolic goals are often individualized. Considering the generally young age of the participants, the short duration of diabetes, and the low prevalence of coexisting conditions, we think that the unitary glycated hemoglobin goal used in this trial was clinically appropriate.

A limitation of our trial is the exclusion of thiazolidinediones and the SGLT2 inhibitor class of glucose-lowering medications, owing to safety concerns at the time of planning and the timing of FDA approval, respectively. Although the selection of single agents within the four medication classes facilitated the conduct of the trial, this selection limited extrapolation of the current results to other medications within the classes. The trial was unblinded for practical reasons; however, the metabolic outcomes were measured routinely and objectively in all the participants, reducing any potential bias of ascertainment. Finally, medication adjustments were carried out frequently in accordance with the protocol, a practice that may not reflect the slow rate of medication adjustments in the clinical setting.[24]

The major implication of the current trial is that maintenance of target glycated hemoglobin levels is challenging, even in a clinical trial in which all care is provided free of charge. The data highlight the need for more effective interventions for long-term control of glycemia in persons with type 2 diabetes. Comparative-effectiveness studies are rarely performed by industry. Our trial presents a clear and objective comparison of the advantages and disadvantages of four commonly used glucose-lowering medications, added to metformin, and these findings should help guide the choice of medications used in the treatment of type 2 diabetes. These results can form the basis of shared decision making between providers and patients in selecting the medication to add to metformin. Sitagliptin had less efficacy

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and durability than the other medications, particularly at higher baseline strata of glycated hemoglobin, and these findings as well as the different adverse-event profiles should be considered along with other clinical benefits and costs in selecting medications used to manage hyperglycemia in persons with type 2 diabetes.

All four medications (glargine, glimepiride, liraglutide, and sitagliptin) improved glycated hemoglobin levels when added to metformin. However, glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target glycated hemoglobin levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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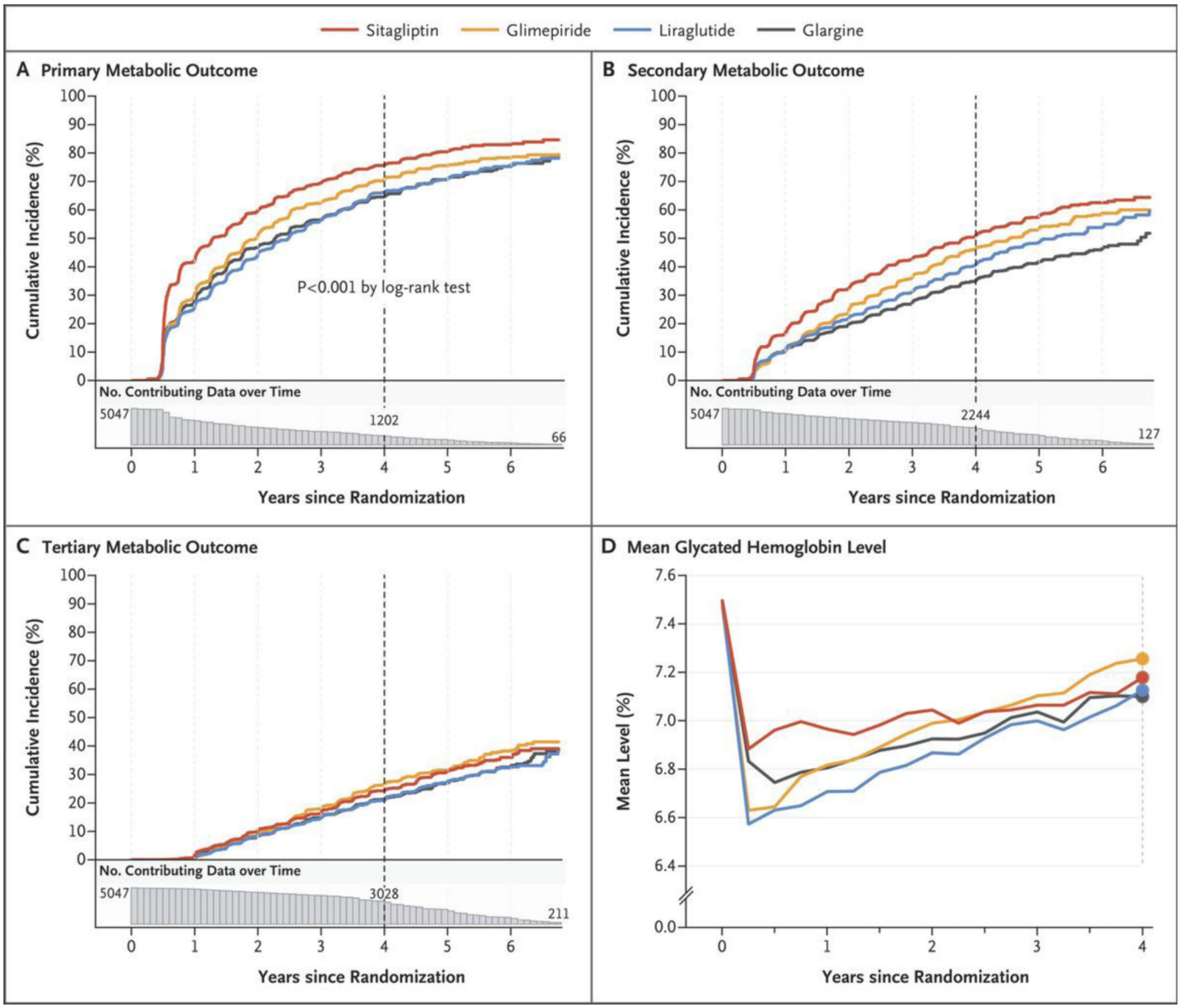

Figure 1. Kaplan–Meier Analysis of Outcome Events and Mean Glycated Hemoglobin Levels.

Shown are the cumulative incidences of a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome) (Panel A), a glycated hemoglobin level of greater than 7.5% (the secondary metabolic outcome) (Panel B), and a confirmed glycated hemoglobin level greater than 7.5% after the secondary outcome (the tertiary metabolic outcome) (Panel C), as well as the mean glycated hemoglobin levels (Panel D). In Panels A through C, the shaded bars along the x axis indicate the number of participants with data available for the analyses over time (i.e., the number of participants in whom a specified outcome event had not developed by that time). The vertical dashed lines indicate the results at 4 years, when 85.8% of the participants were undergoing follow-up. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.5.

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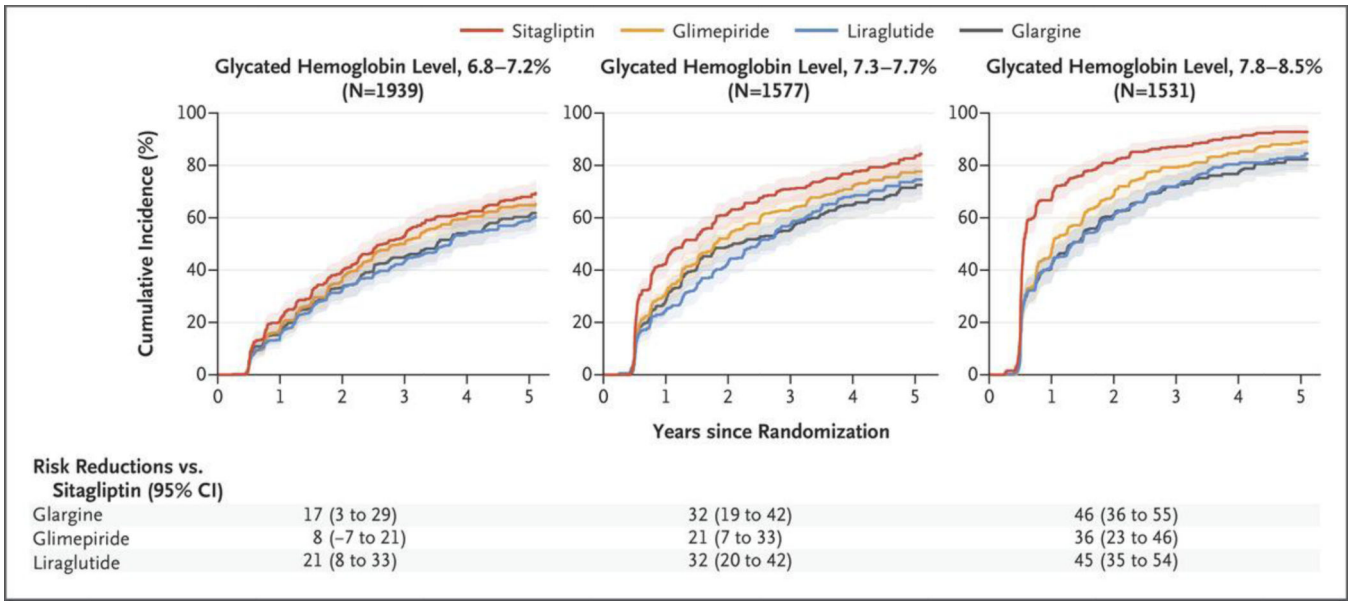

Figure 2. Analyses of the Primary Outcome According to Baseline Glycated Hemoglobin Levels.

The risk reductions, calculated from the hazard ratios, with glargine, glimepiride, and liraglutide, as compared with sitagliptin, are shown with unadjusted 95% confidence intervals. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.5.

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Adverse Event	Glargine (N=1263)		Glimepiride (N=1254)		Liraglutide (N=1262)		Sitagliptin (N=1268)		Pairwise Treatment Comparisons
	no. of participants (%)	*event rate (95% CI)*	*no. of participants (%)*	*event rate (95% CI)*	*no. of participants (%)*	*event rate (95% CI)*	*no. of participants (%)*	*event rate (95% CI)*	
Death	42 (3.3)	0.65 (0.47–0.87)	43 (3.4)	0.67 (0.48–0.90)	27 (2.1)	0.42 (0.27–0.60)	41 (3.2)	0.63 (0.45–0.86)	None are significant
Severe hypoglycemia	16 (1.3)	0.32 (0.19–0.49)	28 (2.2)	0.61 (0.43–0.84)	12 (1.0)	0.21 (0.11–0.35)	9 (0.7)	0.16 (0.08–0.29)	
Any adverse event	468 (37.1)	15.3 (14.3–16.3)	480 (38.3)	16.0 (15.0–17.0)	427 (33.8)	13.7 (12.8–14.7)	452 (35.7)	14.9 (13.9–15.8)	
Weight gain	166 (13.1)	3.0 (2.6–3.5)	152 (12.1)	2.8 (2.3–3.2)	77 (6.1)	1.3 (1.1–1.7)	115 (9.1)	2.0 (1.7–2.4)	
Gastrointestinal symptoms	451 (35.7)	16.5 (15.0–18.0)	422 (33.7)	15.1 (13.7–16.6)	551 (43.7)	22.9 (21.0–24.9)	435 (34.3)	15.1 (13.7–16.6)	

I Glargine G Glimepiride L Liraglutide S Sitagliptin

····· P≤0.05 --- P≤0.01 — P≤0.001 No statistical difference

Figure 3. Overall Incidence of Adverse Events.

Event rates were calculated as the number of events per 100 participant-years. Simple P values (not corrected for multiple tests among event types or treatment groups) were obtained from a Poisson regression model of the rates. The diagram denotes the range of the P values for the six pairwise group comparisons of each adverse event. The following were adjudicated events: serious adverse events or any targeted events, including severe hypoglycemia, lactic acidosis, pancreatitis, diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome, revascularization (coronary, peripheral, or cerebral), congestive heart failure, or cancer. The first occurrence of weight gain of 10% or more was compared with the baseline weight. Gastrointestinal symptoms included any one of the following symptoms that occurred at least once per week in the 30 days before the quarterly visit and were reported by the participant: nausea, vomiting, bloating or stomach pain, or diarrhea.

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Table 1.

Protocol Completion and Adherence in the Treatment Groups during the Trial.

Variable	Glargine (N = 1263)	Glimepiride (N = 1254)	Liraglutide (N = 1262)	Sitagliptin (N = 1268)
Retention — no./total no. (%) [*]	1138/1221 (93.2)	1142/1211 (94.3)	1156/1235 (93.6)	1144/1227 (93.2)
Overall adherence to trial visits — % [†]	91.4	92.9	92.3	92.8
Mean follow-up — yr [‡§]	4.9±1.4	5.0±1.3	5.0±1.3	5.0±1.3
Discontinuation of metformin — no. (%)	105 (8.3)	98 (7.8)	88 (7.0)	97 (7.6)
Use of nontrial, glucose-lowering medications outside the protocol, discontinuation of assigned trial treatment outside the protocol, or both — no. (%) [¶]	332 (26.3)	426 (34.0)	368 (29.2)	347 (27.4)
<1 yr after randomization	65 (5.1)	61 (4.9)	150 (11.9)	60 (4.7)
1 to <2 yr after randomization	51 (4.0)	65 (5.2)	51 (4.0)	60 (4.7)
≥2 yr after randomization	216 (17.1)	300 (23.9)	167 (13.2)	227 (17.9)
Duration of assigned trial treatment in accordance with the protocol — yr [§¶‖]	4.3±1.8	4.2±1.7	4.1±2.0	4.3±1.7
Percentage of trial time during which participant received originally assigned treatment in accordance with the protocol [§¶‖**]	83.7±28.9	82.0±28.7	79.1±34.6	84.0±27.7
Discontinuation of assigned trial treatment outside the protocol — no. (%) [¶]	172 (13.6)	294 (23.4)	289 (22.9)	236 (18.6)
Maximum dose of assigned treatment received [††‡‡]	51.4±39.7 U	5.4±2.8 mg	1.6±0.5 mg	98.4±12.2 mg
Use of nontrial glucose-lowering medication outside the protocol — no. (%)	176 (13.9)	208 (16.6)	136 (10.8)	193 (15.2)

[*] Retention was defined as completion of the trial closeout visit. The denominators in this row sum to 4894 (i.e., participants who were not known to have died before the end of the trial).

[†] Visit adherence was calculated for each participant as 100% multiplied by the number of trial visits attended, divided by the maximum number of trial visits according to either the expected closeout trial visit date in participants who survived to the end of the trial or the date of death.

[‡] The duration of follow-up was calculated as the date of last trial contact minus the date of randomization.

[§] Plus–minus values are means ±SE.

[¶] Participants were considered to have received assigned treatment if treatment was discontinued in accordance with the trial protocol (e.g., the randomized medication was discontinued because the participant had a tertiary outcome event, as stated in the protocol).

[‖] The duration shown is the time from randomization to the date of first discontinuation of trial treatment, use of nontrial glucose-lowering medication, or both in participants who discontinued trial treatment, used nontrial glucose-lowering medication during the trial, or both, or the time from randomization to the date of the last trial contact in those who did not discontinue trial treatment, did not use nontrial glucose-lowering medication during the trial, or both.

[**] The denominator for this percentage is the time from randomization to expected closeout visit date in participants who survived to the end of the trial, or the time from randomization to death, calculated for each participant.

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†† Shown is the mean maximum dose of randomly assigned medication taken at any time during the trial.

Plus–minus values are means ±SD.

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Table 2.

Primary and Secondary Metabolic Outcomes.*

Outcome	Glargine (N = 1263)	Glimepiride (N = 1254)	Liraglutide (N = 1262)	Sitagliptin (N = 1268)
Primary metabolic outcome†				
Participants — no. (%)	852 (67.4)	908 (72.4)	860 (68.2)	981 (77.4)
Rate/100 participant-yr (95% CI)	26.5 (24.8–28.4)	30.4 (28.4–32.4)	26.1 (24.4–27.9)	38.1 (35.8–40.6)
Pairwise hazard ratios (95% CI)				
Glargine	—	0.89 (0.81–0.98)‡	1.02 (0.93–1.12)	0.71 (0.64–0.78)§
Glimepiride	—	—	1.15 (1.04–1.27)¶	0.79 (0.72–0.88)§
Liraglutide	—	—	—	0.69 (0.63–0.76)§
Hazard ratio in the treatment group as compared with all other treatments combined (95% CI)	0.87 (0.80–0.94)§	1.01 (0.93–1.09)	0.84 (0.78–0.91)§	1.37 (1.27–1.48)§
Restricted mean survival time over 4 yr of follow-up (95% CI) — days	861 (831–891)	809 (780–838)	882 (853–911)	697 (667–726)
Secondary metabolic outcome‖				
Participants — no. (%)	498 (39.4)	633 (50.5)	583 (46.2)	697 (55.0)
Rate/100 participant-yr (95% CI)	10.7 (9.8–11.7)	14.8 (13.6–16.0)	13.0 (12.0–14.1)	17.5 (16.3–18.9)
Pairwise hazard ratios (95% CI)				
Glargine	—	0.73 (0.65–0.82)	0.83 (0.73–0.93)	0.61 (0.54–0.69)
Glimepiride	—	—	1.13 (1.01–1.27)	0.84 (0.75–0.93)
Liraglutide	—	—	—	0.74 (0.66–0.83)
Hazard ratio in the treatment group as compared with all other treatments combined (95% CI)	0.72 (0.65–0.79)	1.09 (1.00–1.20)	0.92 (0.84–1.01)	1.38 (1.26–1.51)
Restricted mean survival time over 4 yr of follow-up (95% CI) — days	1188 (1163–1212)	1115 (1090–1141)	1154 (1129–1179)	1030 (1002–1058)

*Shown are the numbers of participants with primary and secondary metabolic outcome events according to randomized treatment group (intention-to-treat) with overall rates and hazard ratios. Calculations for the tertiary outcome are provided in Table S5. CI denotes confidence interval.

†For the primary outcome, P values were obtained from closed testing of pairwise group differences corrected for six pairwise comparisons. Confidence limits corrected for six pairwise tests were obtained by inverting the closed-testing z-test value and then computing corrected 95% confidence intervals. P<0.001 from a test of the log hazard ratios for treatment failure among the four treatment groups, with the use of a Cox proportional-hazards model, with treatment group as the only predictor variable.

‡P≤0.05 for the specified comparison of two treatment groups.

§P≤0.001 for the specified comparison of two treatment groups.

¶P≤0.01 for the specified comparison of two treatment groups.

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‖For the secondary outcome, confidence intervals obtained from the Cox proportional-hazards model are not corrected for multiple comparisons among groups.